<Division of Synthetic Chemistry>Synthetic Organic Chemistry

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– Synthetic Organic Chemistry –

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Scope of Research

The research interests of the laboratory include the development of advanced molecular transformation, total synthesis of biologically active products, and molecular recognition. Programs are active in the areas of asymmetric alkylation of carbonyl compounds based on “memory of chirality”, organocatalysis for fine organic syntheses, synthesis of unusual amino acids and nitrogen heterocycles, regioselective functionalization of carbohydrates, and the structural and functional investigation of heterochiral oligomers.

KEYWORDS

Organocatalysis
Regioselective Functionalization
Dynamic Chirality
Unusual Amino Acid
Molecular Recognition

Selected Publications

Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata,T.; Schedel, H., A Catalytic One-Step Process for the Chemo- and Regiocelective Acylation of Monosaccharides, *J. Am. Chem. Soc*., **129,** 12890-12895 (2007).

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Kawabata, T.; Jiang, C.; Hayashi, K.; Tsubaki, K.; Yoshimura, T.; Majumdar, S.; Sasamori, T.; Tokitoh, N., Axially Chiral Binaphthyl Surrogates with an Inner N-H-N Hydrogen Bond, *J. Am. Chem. Soc*., **131,** 54-55 (2009).

Yoshida, K.; Furuta, T.; Kawabata, T., Organocatalytic Chemoselective Monoacylation of 1,n-Linear Diol, *Angew. Chem. Int. Ed*., **50,** 4888-4892 (2011).

Hamada, S.; Furuta, T.; Wada, Y.; Kawabata, T., Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts, *Angew. Chem. Int. Ed*., **52,** 8093-8097 (2013).

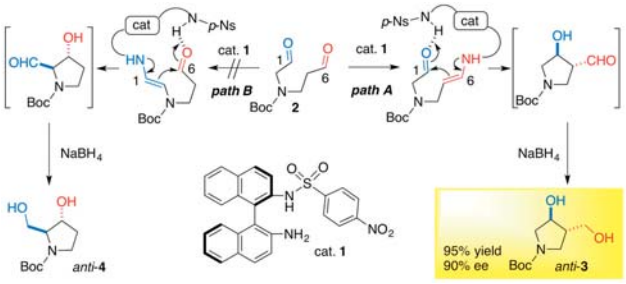
Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T., Asymmetric α-Arylation of Amino Acid Derivatives by Clayden Rearrangement of Ester Enolates via Momory of Chirality, *J. Am. Chem. Soc*., **135,** 13294-13297 (2013).

Yoshimura, T.; Tomohara, K.; Kawabata, T., Asymmetric Induction via Short-Lived Chiral Enolates with Chiral C-O Axis, *J. Am. Chem. Soc*., **135,** 7102-7105 (2013).

Regio- and Stereoselective Intramolecular Cross-Aldol Reaction of Dials Promoted by Catalysts with "Low" Reactivity

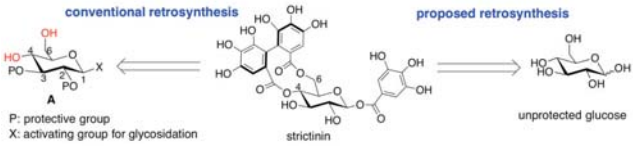
Intramolecular direct cross-aldol reactions of 1,n-alkanedials have high potential in preparing bioactive natural products and pharmaceuticals such as prostaglandins and nucleic acid medicines. To achieve this reaction selectively, not only stereochemistry but also regiochemistry of the products has to be controlled (Figure 1, path A *vs*. path B). In amine-catalyzed reactions based on the enamine mechanism, high regioselectivity is expected only under the conditions that the amine catalyst precisely discriminates two enolizable formyl groups and convert them individually to the aldol donor (enamine component) as well as the aldol acceptor (carbonyl component), selectively.

Axially chiral catalyst **1** having aniline-type amine was employed under the postulation that catalysts with intrinsic low reactivity could readily discriminate the formyl groups and control the regioselectivity during the cross-aldol reaction. As expected, catalyst **1** could distinguish the formyl groups of **2** efficiently to realize the reaction through the enamine of C(6)-formyl group (path A). *Anti*-**3** was obtained as a sole product in high regio- and stereoselectivities, while *anti*-**4** via the enamine of C(1)-formyl group (path B) was not detected.



A New Retrosynthetic Approach towards Total Synthesis of Natural Glycosides via Catalyst-Controlled Regioselective Acylation

Natural glycosides have attracted considerable interests as synthetic targets due to the pharmaceutical potentials based on their significant biological activities including anti-HSV, anti-influenza virus, anti-tumor, and neuroprotective activities. Total synthesis of strictinin, a biologically active natural glycoside, is shown here. A conventional retrosynthetic analysis should lead to suitably protected precursor **A**, possessing free C(4)-OH and C(6)-OH (shown in red) and C(1)-X (X : activating group for glycosidation), C(2)-OP (P : protective group), and C(3)-OP to introduce a hexahydroxy diphenoyl (HHDP) group at C(4)-O and C(6)-O of the glucopyranose skeleton. In contrast, we propose a new retrosynthetic approach towards the total synthesis employing unprotected glucose as a direct precursor.



We found that glycosidation of a gallic acid derivative using unprotected glucose as a glycosyl donor took place in a highly β-selective manner under Mitsunobu conditions to give glycoside **6** in 78% yield. Treatment of **6** with anhydride **7** in the presence of catalyst **5** followed by a condensation agent (DMC, DMAP) gave 4, 6-digallate **8** in 51% yield. The first introduction of a galloyl group at the inherently less reactive C(4)-OH was assumed to proceed via catalyst-controlled regioselective acylation, and the second introduction of a galloyl group at the most reactive primary C(6)-OH proceeded via substrate-controlled regioselective acylation. Thus, overall 5-step total synthesis of natural glycoside, strictinin, was achieved from naturally abundant glucose without using any protective groups for glucose. The overall number of the steps for the total synthesis is much less than those previously reported (11 or 13 steps from glucose). Similarly, total syntheses of natural glycosides, tellimagrandin II (eugeniin), and pterocarinin C have been performed in six steps from glucose.